(54) Title: NEW USE OF BIOACTIVE SILICIOUS GLASS AND NEW COMPOSITIONS CONTAINING BIOACTIVE SILICIOUS GLASS
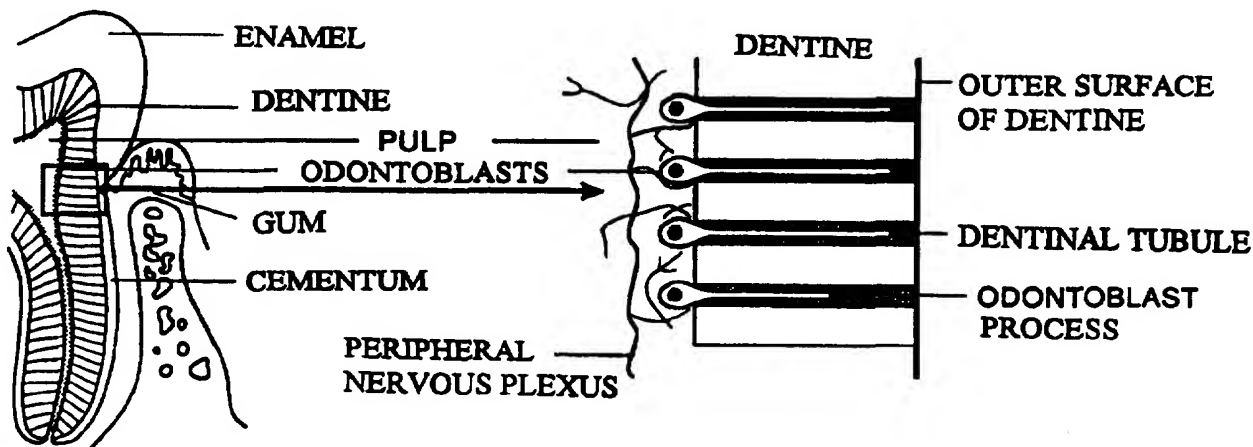
(57) Abstract

The invention concerns a novel use of bioactive silica containing glass. According to the present invention, the said glass is used for making a preparation which reduces the pulpal irritation of a tooth and/or strengthens the structure of a tooth. The invention also presents a pharmaceutical preparation, including a glass phase which is bioactive silica containing glass in the form of a paste, suspension or solution mixed in a physiologically suitable liquid or bound to a physiologically suitable vehicle, and which preparation reduces the pulpal irritation of a tooth and/or strengthens the structure of a tooth. Bioactive silica containing glass may be a material which contains only Si-oxide or Si-hydroxide and which allows the formation and movement of Si-OH-groups. Preferably, the preparation also comprises calcium and phosphate sources.

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New use of bioactive silicious glass and new
compositions containing bioactive silicious glass.

The aim of this invention is to introduce a novel use of
bioactive glass and new preparations comprising bioactive
silica containing glass. The said preparations can be used
for reinforcing a tooth and for closing the dentinal
5   tubules in the dentine in order to reduce pain transmitted
to the pulp as a consequence of open tubules.

Dentine forms the frame of a tooth. It surrounds the pulp
and is covered by enamel on the crown and cementum on the
root. The cementum does not always meet the edge of the
10 enamel at the cementum-enamel junction. In such cases,
dentine, which is not protected by another type of hard
tissue, is exposed at the neck of a tooth. In the young,
this area is usually covered by gingiva which covers this
particular zone of dentine and prevents its exposure to
15 irritation from the oral cavity.

Dentine consists of an extracellular matrix, which is
formed by odontoblasts lining the pulp cavity. When dentine
is formed and it becomes thicker, each odontoblast leaves
behind a cell extension i.e. an odontoblast process. These
20 processes remain inside the developing tissue and form
dentinal tubules, which extend from the enamel-
dentine/cementum-dentine border into the pulp. When
exposed, open dentinal tubules form a link between the
dentine surface and the pulp.

25 The structure of dentine is shown in detail in Figure 1.

Once the tooth has stopped growing, odontoblasts continue
their function and form secondary dentine on the pulp side
of the tooth. They also form hard tissue i.e. intratubular
dentine which gradually closes the tubules around the
30 receding odontoblast processes (Figure 2.). The level of

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mineralisation of intratubular dentine is significantly
higher than that of intertubular dentine. The
mineralisation of dentinal tubules is a very slow but
natural process, associated with the ageing of a tooth. The
5   slow pace and unpredictability of the process are
manifested as problems in various clinical situations.

The hydrodynamic pain transmission mechanism of exposed
dentine can be described as follows:

Dentinal tubules are 1 - 2 μm in diameter. When a section
10 is cut perpendicular to the dentine surface, there are
around 30 000–40 000 dentinal tubules per mm^2. A dentinal
tubule is filled with an odontoblast process, surrounded by
fluid from the pulp. A very strong capillary force prevails
in open and exposed dentinal tubules. Consequently, fluid
15 mechanically removed from the opening of the tubule is
quickly replaced by fluid flowing out from the pulp.
Similarly, substances with strong osmotic pressure (e.g.
sweet solutions) cause an outward flow of fluids in the
tubule, which in turn, leads to transformations of the
20 odontoblasts lining the pulp chamber and tissues
surrounding ondontoblasts, thus activating the nerve
endings. On the other hand, irritation transmitted to the
pulp may be caused by the inward flow of the fluid in the
dentinal tubule. In practice, the hydrodynamic mechanism
25 refers to the fluid flow in a dentinal tubule caused by a
stimulus and the resulting hydraulic vibration in the pulp.
According to current opinion and experience, the closing of
the tubule and the resulting complete or partial prevention
of fluid flow would lead to a reduction or even elimination
30 of nerve activation, sensed as pain regardless of the
primary stimulus (1). The pain transmission mechanism is
illustrated in Figure 3.

Clinical problems:

The exposure of dentine and dentinal tubules leading to the

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pulp may be the result of caries. The hard tissue
(enamel/cementum) protecting the dentine is destroyed
during the decay process. The situation leads to the known
painful symptoms associated with cavity formation. The pain
5 results from irritation which is transmitted to the pulp
nerve endings through the dentinal tubules. During the
decay process, partial mineralisation of tubule contents is
usually observed. This is a consequence of the high calcium
and phosphate ion concentration caused by demineralisation
10 processes of the enamel and dentine in the close vicinity
of intact dentine tissue. Strengthening of this phenomenon
and its incorporation into the properties of filling
materials would be desirable.

Exposure of dentine is also often associated with the
15 periodontal diseases of a tooth, and also with the normal
ageing process and dental hygiene habits. In certain cases,
even in the young, the gingiva recesses or teeth erupt so
that the necks of the teeth become exposed. This itself may
lead to strong painful symptoms, in patients whose dentine
20 was not covered by the protective and non-sensitive
cementum in the first place. More often, however, exposure
of dentine is associated with wrong toothbrushing habits,
either using too heavy a hand, a coarse brush or the wrong
technique. This results in worn and hypersensitive teeth,
25 which affects the person's tolerance of
hot/cold/bitter/sweet drinks and food, makes breathing more
difficult in the hot and cold, and also interferes with
proper oral hygiene.

Infections in the periodontal tissues and, especially, the
30 treatment of periodontal infections, generally lead to
gingival recession and exposure of dentine, often of fairly
large areas. As successful therapy involves the removal of
the root cementum protecting dentine, and polishing, which
wears the teeth further, it is obvious that the general
35 consequence of such treatment (25%) is the exposure of
tooth necks and hypersensitivity. If the patient is fairly

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elderly and their dentinal tubules exhibit a substantial
layer of highly mineralised intra-tubular dentine, the
post-treatment pain is less severe. On the other hand, the
pain resulting from the treatment may, in certain cases, be
5   strong, it can continue for weeks and may require the use
of analgetics. In the most extreme cases, irritation may
lead to infection and, subsequently, to the death of a
tooth and root canal treatment. In association with dental
care, hypersensitive teeth is an irritating problem which
10 occurs frequently, and should have a simple and inexpensive
cure (2). Figure 4 shows a tooth and the area with the
exposed dentinal surface.

Known methods of treatment:

Tooth ache, resulting from cavity formation refers,
15 regardless of its similarities to hypersensitive dentine,
to a different problem area. Sensitivity associated with
caries, and pain caused by irritation is usually treated by
fillings. At the bottom of the prepared cavity, a
commercially available preparation is placed against the
20 pulp, the biologically active component of such preparation
is usually calcium hydroxide ($CaOH_2$). At the cell level, the
strongly alkaline calciumhydroxide first induces
irritation, which leads to the necrotisation of the tissue.
Over a longer time span, however, it promotes the healing
25 process. The result of the treatment is the formation of
reparative secondary dentine. The formed tissue layer
separates the pulp from the damaged area or the filling,
but its effect on the mineralisation of dentine tubules is
minimal.

30 During filling, the dentinal tubules can also be closed by
glass ionomer cement, or with different preparations based
on polymer chemistry (binder plastics, resins, dentine
adhesives). These substances close dentinal tubules
mechanically and improve the retention of the filling being
35 prepared. Fluoride which is released from the glass ionomer

cement may, in theory, have a positive effect on the
mineralisation process of dentinal tubules. However, there
are no research results of the possible clinical role of
this phenomenon. Plastic-based preparations have no
5   biological effects which promote the healing process and/or
the formation of hard tissue between the pulp and the
damaged and restored area.

The epidemiological data describing the extent of the
problem caused by hypersensitive dentine and the need for
10 its treatment is limited. In practice, dentine
hypersensitivity is a common and typically highly variable
problem. Because the symptoms are linked closely to the
behaviour of a person and, in the long run, disappear; and
because there are commercially available toothpastes, which
15 may lower the sensitivity, the actual extent of the problem
is difficult to define solely on the basis of how often
people seek for professional help at their dentist's for
this particular problem. In association with the treatment
of inflamed gingivae and supportive tissues of the teeth,
20 the need to offer relief for hypersensitive teeth is often
acute.

Nowadays, two different concepts of treatment for
hypersensitive teeth are available. These treatments are
based on either raising the pain threshold of a tooth, or
25 on the formation of a protective mineralisation precipitate
either on the surface of a tooth or, preferably, in the
dentinal tubules. In addition, the treatment involves
gentle (possibly chemical) plaque control, diet guidance
and confirmation that the irritation threshold of the pulp
30 is not lowered by masticational overload or a poor filling
which maintains chronic infection in the pulp.

For a long time, some toothpastes have contained substances
designed to give relief to hypersensitive teeth (3, 4, 5,
6). The goal has been either the denaturation
35 (formaldehyde) of the contents of the dentinal tubule or

the formation of mineral precipitates (strontium chloride, fluorides, abrasives).

Sodiumfluorophosphate may infact have some therapeutic effects. Potassiumnitrate and potassiumcitrate reduce the

5   irritability of the pulpal nerves without affecting the actual contents of the dentinal tubules (7). The problem with substances which merely raise the activation level of nerve endings (including corticosteroids) is that they do not strengthen the tooth and the pulp remains exposed to

10 hydrodynamic irritation even after treatment. Consequently, the therapeutic effect of such treatment only lasts for a short time. Research results concentrating on the therapeutic effects of toothpastes are highly contradictory. On one hand, placebo effects, and on the

15 other hand, pain relieving effects up to 80% have been reported. Generally, the problem with toothpastes is that they act very slowly, often only after several weeks of use. Thus, toothpastes may be suitable for home treatment of subacute problems. It is, however, necessary to find

20 more powerful and quicker-acting methods for acute pain.

In clinical situations, today, the most common method for treating hypersensitive teeth is to use fluorides - either sodiumfluoride or tin fluoride in 2-10% mixtures (8, 9, 10). Fluoride can also be applied topically to the surface

25 of a tooth in combination with varnish-based substances (Duraphat (11)). The varnish prolongs the effect of fluoride, and at the same time, the varnish itself may have some tubule blocking effect. At least over a short time-span, fluoride preparations have been shown to have

30 positive therapeutic effects. Recently, some attention has been paid to the acidity of these preparations and irritation related to this acidity. It is thought, however, that problems caused by the acidity in the pulp can be relieved by alternating the use of calciumhydroxide and

35 fluoride. This treatment has been empirical. In principle, results have been positive. Objective research data of the

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effects of the treatment or its permanence is not
available. The presence of alkaline calciumhydroxide may,
however, complicate the formation of the practically
insoluble, and therefore, desired tinfluorophosphate; and
5   instead, favour the formation of calciumfluoride which
dissolves in neutral environment. In such conditions, the
treatment may be effective, but temporary.

Solutions which assist the remineralisation of the tooth
surface may also reduce sensitivity when used for long
10 enough. Due to their watery nature and slow effect, this
method — or those with the toothpastes — is not very good
for the treatment of acute pain. For example, two
mineralisation solutions — A and B — have been used.
Solution A contains 6 mM PO_4 and B mM Ca. In addition, both
15 solutions contain 0.15 mM NaCl and 5 ppm F. 10 ml of
solution A and 10 ml of solution B are mixed in a glass
immediately before use. The mixture of mineralisation
solution, diluted in water is rinsed in the mouth for 1 - 2
minutes, and spat out. It is recommended that this
20 procedure is repeated twice a day preferably after tooth
brushing.

Potassiumoxalate ($K_2C_2O_4$ or KHC_2O_4, 3 - 30%) has also been
used in the treatment of hypersensitive teeth. The idea
behind the use of these chemicals as a therapeutical agent,
25 is based on the ability of oxalate to precipitate calcium
residing on the surface of a tooth or in the dentinal
fluid. In this reaction, crystals which obstruct the
transmission of hydraulic stimulus from the tooth surface
into the pulp, are formed. A major part of the precipitate
30 thus obtained usually dissolves within a week, but the
diameter of dentinal tubules remain smaller than before
treatment. Long-term effects of the treatment are still to
be confirmed (3, 12, 13). More permanent results have been
obtained with ferro-oxalate (6%) than with other oxalate
35 treatments (14). At least one research report, however, has

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found acidic table salt solutions more effective than oxalate against hypersensitive teeth.

Products base on plastic polymers (resins, dentine adhesives) and cyanoacrylate effectively block dentinal
5 tubules (15). At least over a short time-span, they remove pain and protect the pulp from the immediate irritation. These substances, however, cannot be regarded as biological, since they do not lead to a natural healing process and to the mineralisation of dentinal tubules.
10 Dentine adhesives have also been found to be highly allergenic. The dental care personnel, however, are the major target of their allergenic effect. Additionally, acrylate, meta-acrylate and cyanoacrylate compounds have been found to be irritants, and also genotoxic and
15 carcinogenic both in animal experiments and cell culture studies. Plastic-based "coating" also forms a microbe retentive surface at the area of gingiva-tooth junction which easily leads to the recurrence of the recently treated disease. Thus, the use of dentine adhesives,
20 especially in periodontal patients, cannot be regarded as meaningful. When considering filling materials, glass ionomer cement has also been proposed for the treatment of hypersensitive teeth (11). Advantages of glass ionomer cement are its properties to bind dentine and to release
25 fluoride. In practice, glass ionomer cement is difficult to use, especially in the treatment of widely exposed dentine. However, it is suitable for the treatment of distinctly defined and relatively deep abrasion lesions which are found clearly above the gingiva margin.

30 Older literature suggests that dentinal tubules should be blocked by using silver nitrate. The results of using this substance have been highly variable. In addition, silver nitrate is a highly staining agent. The treatment of root surfaces first with zinc chloride and then with potassium
35 ferrocyanide have also been proposed. The treatment yields a protective precipitate on the surface of a tooth. The

results have been reported to be satisfactory. If swallowed by mistake, however, the agent is toxic.

The use of a NdYAG laser has been proposed as a potential new approach for closing the dentinal tubules. Preliminary
5 results with this treatment are promising. The mechanism behind the treatment, the permanence of the treatment and its possible adverse effects on the pulp are still to be confirmed.

The heterogeneity of possible treatments presented above,
10 gives a good picture of a dentist's real and realistic choices in the effective treatment of hypersensitive teeth. Even after several years of experiments, none of the offered alternatives has proved to be any better than the other, and thus a predominant method of treatment. Common
15 to all the offered methods, is that they do not consciously aim at producing an apatite-based compound $(Ca_{10}(PO_4)_6X_2$, in which X is either a hydroxyl or fluoride) — chosen by nature — to close the dentinal tubules. Generally, the goal has been to make any type of precipitate to block the
20 dentinal tubules as quickly as possible (3, 16, 17). None of the tested methods of treatment has aimed at contributing to the crystallisation process itself, by simultaneously adding calcium and/or phosphate which essentially participates in the formation of
25 precipitate/crystals. Therefore, at the background of the partly contradictory results reported may be the availability of these essential ions during the short period of treatment. On the other hand, some of these treatments have sought results through the cumulative
30 effects of short-term application (e.g. toothpastes and remineralisation solutions). An exception to these treatment concepts is the use of fluoride containing preparations, although their effect is not based on increasing the availability of calcium or phosphate on the
35 area to be treated.

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The purpose of the present invention is to eliminate the
above mentioned problems and present a new, effective
preparation for reducing or inhibiting pulpal irritation
i.e. hypersensitivity of a tooth. The preparation also
5   provides a new method for effectively strengthening a
tooth.

The characteristic features of this invention are presented
in the independent claims.

This invention concerns a novel use of bioactive silica
10 containing glass for making a preparation which reduces
pulpal irritation and/or strengthens the tooth structure.
This invention also concerns a pharmaceutical preparation
which reduces pulpal irritation and/or strengthens the
tooth structure. The preparation comprises a glass phase,
15 which is bioactive silica containing glass in the form of a
paste, suspension or solution in a physiologically suitable
liquid, or bound to a physiologically suitable vehicle such
as fibrinogen or chitin.

In the following, the term "bioactive silica containing
20 glass" refers to a material comprising Si-oxide or Si-
hydroxide wherein said material allows the formation and
movement of Si-OH-groups. The bioactive silica containing
glass may be, for example, either 1) bioactive glass, which
refers to a mixture of Si-oxide or Si-hydroxide with one or
25 more elements, the elements being: sodium, potassium,
calcium, magnesium, boron, titanium, aluminium, nitrogen,
phosphorous and fluoride; 2) water glass type sodium
silicate; 3) silica gel i.e. Si-hydroxide; 4) solution
comprising Si-OH groups; 5) silica gel comprising Ca, P or
30 6) hydroxyapatite comprising Si-oxide or Si-hydroxide. It
is essential that bioactive silica containing glass allows
the formation and movement of Si-OH groups. It is
recommended that the bioactive silica containing glass also
allows the formation and movement of calcium and phosphate
35 ions.

Figure 5 illustrates a ternary phase diagram of the
bioactive area of certain oxide mixtures. In addition to
SiO_2, CaO and Na_2O, the mixture can, of course, include
oxides together with the elements mentioned in the previous
5 paragraph. Some of the typical bioactive glass compositions
are presented in Table 1.

Table 1. Composition (weight-%) of some bioactive glass
types 1 - 10.

Glass	Type	Na_2O	CaO	P_2O_5	B_2O_3	Al_2O_3	SiO_2
1	S57.5P5	16.00	18.00	5.00	3.00	0.50	57.50
2	S56P6	19.00	16.00	6.00	1.50	1.50	56.00
3	S51P7	20.00	17.00	7.00	3.00	2.00	51.00
4	S53P4	23.00	20.00	4.00	0.00	0.00	53.00
5	S45P7	24.00	22.00	7.00	2.00	0.00	45.00
6	S52P8	25.00	12.00	8.00	0.50	2.50	52.00
7	S46PO	26.00	25.00	0.00	2.00	1.00	46.00
8	S38P8	27.00	23.00	8.00	1.00	3.00	38.00
9	S48P2	28.00	19.00	2.00	1.50	1.50	48.00
10	S55.5P4	29.00	11.00	4.00	0.00	0.50	55.50

20 Bioactive silica containing glass is used in the
preparation in the form of a powder suspended in a
physiologically suitable liquid or is bound to a
physiologically suitable vehicle. The preparation should be
sufficiently moist so that chemical interactions between
25 the glass phase and dentine are maintained.

The glass phase of the preparation may consist solely of
Si-oxide or Si-hydroxide, such as silica gel.
Alternatively, in addition to Si-oxide or Si-hydroxide, the
glass phase may include one or more of the following
30 elements: Ca, P, Na, K, Al, B, N, Mg, Ti or F.

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The suitable composition of a glass phase could be as follows:

	SiO$_2$ or Si-gel	1 - 100%
	CaO	0 - 40%
5	P$_2$O$_5$	0 - 60%
	Na$_2$O	0 - 45%
	K$_2$O	0 - 45%
	MgO	0 - 40%

Although silica gel or water glass type of alkali
10 containing silicate glass can induce the mineralisation of dentine with the help of the calcium and phosphate present in the body fluids, it is advisable to use such bioactive glass compositions which comprise calcium and phosphate. Alternatively, calcium and phosphate containing sources,
15 such as ceramic powder can be added in the preparation.

Suitable binding agents are, for example, fibrinogen or chitin.

The preparation can also comprise substances which promote crystallisation, such as TiO$_2$. Agents assisting
20 crystallisation refer to the agents which contribute to the formation of a crystal or assist in increasing their size.

The preparation is placed in contact with the surface of a tooth, in a periodontal pocket, in a drilled cavity or on a polished surface or otherwise exposed dentinal surface, by
25 covering the area locally or widely with the said preparation. The preparation can then be covered with a protective packing, cementum or with some other corresponding method which prevents the displacement fo the preparation. Figure 6 presents the application of a
30 preparation against the dentine surface.

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A few embodiments of the invention are presented in the following:

When making a temporary filling, it is possible to mineralise (sclerotise) the dentine tubules, by filling the
5   bottom of the cavity cleaned from caries with the bioactive silica containing glass (Figure 7) according to the method presented in this invention. The remaining hard tissue layer will be strengthened and possible pulpal irritation, caused by the permanent filling or its preparation, is
10   reduced. In other words, the tissue layer strengthened with the method described in this invention also serves as an insulating layer. In cases of non-existent or very thin dentine layer, the glass acts as a bioactive surface which favours the formation of secondary dentine. In addition,
15   well mineralised dentine is more resistant to new caries attacks than less mineralised dentine.

The erosion of a tooth refers to a phenomenon in which the surface of a tooth is dissolved by acids which are not produced by bacteria as in the case of caries. Such acids
20   enter the mouth if gastric juice frequently rises to the oral cavity (e.g. acidic burps and bulimia). This may also happen, for example, in the case of heart burn (ulcer), if one eats a lot of citrus fruit and drinks acidic wine or sports drinks. In such situations, the surface of a tooth
25   quickly erodes (Figure 8) and the tooth becomes hypersensitive. By treating the primary disorder and surfaces according to the method of the present invention, two benefits are obtained: hypersensitivity is eliminated and the dentine becomes more resistant to new acidic
30   attacks because of its higher degree of mineralisation. Since the screlotisation of dentine strengthens the tooth against mechanical wear, too, the preparation of this invention can be used for treating other types of attrition damages, for example, those caused by wrong toothbrushing
35   habits.

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In teeth which require root canal treatment, the pulp is
dead and nearly always infected, which results in the
destruction of the bone surrounding the apex of the tooth's
root. With proper treatment, it is possible to keep this
5   kind of a tooth functional. The tooth is, however, more
fragile than a healthy tooth and it cracks and even breaks
easily. By filling the empty root canal temporarily with
the glass paste/suspension of this invention before the
final filling, it is possible to mineralise the dentinal
10   tubules and strengthen the tooth (Figure 9). At the same
time, the method creates a favourable environment for the
healing process of the bone at the apex of the root.

In the crown prosthetics, a tooth is trimmed into the shape
of a conic pillar, on top of which a crown is fitted.
15   During the trimming process, a huge number of dentinal
tubules is exposed, which results in highly sensitive teeth
until the work is completely finished. The trimmed teeth
are covered with temporary crowns during the process.
Temporary crowns can be fixed into place using bioactive
20   silica glass containing paste as a binding agent (Figure
10.). The benefits are the same as with the restorations.
The pillar becomes stronger, hypersensitivity problems
disappear, and when finished, the dentine at the edges of
the prosthetic crown is less susceptible to caries.

25   The obtained clinical effect is based, firstly, on the fact
that the preparation induces crystallisation of apatite in
the dentinal tubules of a tooth; and secondly it promotes
dentine formation as a result of the induction of
odontoblast activity.

30   From the standpoint of desired action, it is preferrable
that the high calcium and phosphate ion concentration is
maintained in close vicinity to the dentinal tubules long
enough to ascertain that the ions are diffused into the
tubules as deep as possible. Actual
35   precipitation/crystallisation is induced by a factor,

called a nucleator, which lowers the energy barrier
preventing the crystal formation and initiates the natural
closing process of dentinal tubules. In the present
invention, the nucleator, as well as the ions contributing
5   to the composition of the precipitate and the crystal size,
are brought from outside by keeping the active silica
containing glass in contact with the tooth.

Nucleation:

Mineralisation as a biological phenomenon is complex and
10 difficult to control. To understand its fundamental
mechanism, mineralisation is a target of intensive and
continuous study. One of the basic features relating to
mineralisation, is that although serum and tissue fluids
are supersaturated solutions with regard to calcium and
15 phosphate, spontaneous crystallisation does not take place
in tissues. Thus, for example, tissue fluid or other
solutions with equivalent concentrations of calcium and
phosphate can be kept in a test tube for an endlessly long
time without any crystal formation. If a tiny crystal of
20 hydroxyapatite is then added into the test tube, the
crystal starts to grow at the expense of the calcium and
phosphate in the solution. Crystallisation is not initiated
without assistance because the condensation of the ion
clusters, which is the prerequisite for the formation of a
25 crystal nucleus, requires energy as chemical reactions
generally do. Crossing the threshold requires special
conditions and/or an outside factor (nucleator).

In principle, the initiation of crystallisation, i.e. the
formation of an crystal nucleus, can be assisted in three
30 ways:

1) The amount of inorganic ions can be increased, so that a
certain critical number of ion clusters are formed locally
and simultaneously in a small space. Under these
conditions, the energy threshold preventing the

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condensation of any of the ion clusters may be crossed. The
formed crystal nuclei progresses the crystallisation either
by growing in size itself or acting as a nucleator for the
other still labile ion clusters around it (secondary
5   nucleation). If the crystal formation is initiated as
described above, it is called homogenic nucleation.

2) With the presence of a factor (nucleator) which lowers
the energy threshold preventing the formation of a crystal
nucleus, it is not necessary to increase ion concentration.
10   If the crystal formation is initiated with the help of an
outside nucleator, it is called heterogenic nucleator.

3) There are also agents which raise the energy threshold
thus preventing the formation of a crystal nucleus. One of
the most well-known of these agents is pyrophosphate.
15   Consequently, the removal or inactivation of such a
locally-acting inhibitor may assist mineralisation.

Once a crystal nucleus has formed, it continues to grow so
that new ions continuously diffuse from the solution onto
the surface of the crystal. In a normal biological
20   environment, the mineralisation of connective tissue also
involves cell activity. The cells build a mineralisation
frame formed by the extra cellular matrix. At least at the
beginning of the mineralisation process, small membrane
lining structures (matrix vesicles) can be seen on the
25   surfaces of the cells forming hard tissue. The vesicles
contain calcium binding lipids and alkaline phosphatase. It
is thought that it is specifically these conditions that
are especially favourable for the formation of the first
crystal nuclei. Once the crystal nucleus has formed, the
30   vesicle bursts and the crystal leaves the interior of the
cell and becomes a building block for hard tissue. Since
these vesicles only appear at the beginning of the hard
tissue formation, it is apparent that there must also be
other mechanisms which lead to the mineralisation of a
35   tissue. In fact, the extracellular matrix contains quite a

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few organic molecules which may act as nucleators, at least, *in vitro*. These molecules include, for example, osteonectin, phosphoproteins, collagen, anionic phospholipids and sulphur containing compounds such as
5 chondroitinsulphate and ceratansulphate.

Alkaline phosphatase is always found where hard tissue is formed. Its role in the formation of hard tissue is not completely clear. It is obvious, however, that it is an enzyme, which in the alkaline environment participates both
10 in the hydrolysation of different organic compounds and in the release of phosphate ions.

Intratubular dentine does not contain an actual mineralisation frame (organic matrix). This is shown when demineralised tooth samples are prepared and dentinal
15 tubules appear hollow at those sites which were filled with intratubular dentine. This does not exclude, however, the involvement of nucleators in the mineralisation of intratubular dentine. The situation appears to be just the opposite, because odontoblasts and/or their processes are
20 known to respond to certain stimuli and are able, at least to some extent, to accelerate the formation of protective intratubular dentine. It is also possible, however, that the primary stimulus does not stimulate cell activity, but is sufficient to initiate the degeneration of a cell.
25 Consequently, parts of a degenerating cell may act as nucleators. The latter case is, at least partly, indicative of a pathological phenomenon. The third alternative is that certain components of the tissue fluid flowing into the dentinal tubules act as nucleators. This kind of a
30 situation is created, for example, when the cementum layer of the root surface is removed during the treatment of periodontitis and the dentinal tubules are exposed as a wound-resembling surface with open connections to the pulp of the tooth.

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Silica as a nucleator:

The dissolution of silica from the glass type used in the
examples is minimal when the pH of the surface is below 9.
Above this value, its dissolution increases significantly,
5   and is dominant when the pH exceeds 9.5. A characteristic
feature of active glass is that as it increases the pH in
its surroundings, its $Si(OH)_4$ molecules begin to dissolve.
It is clear that when using small granule size in a limited
reaction space, the pH becomes quite high which, in turn,
10 results in an abundant release of silica. In a biological
environment, silica also spreads out into tissues.

The Ca,P layer precipitating on the surface of the glass is
rich in silica over the whole precipitation area. This
suggests that silica has an active role in the formation of
15 the precipitate. Because silica spreads out into the
tissues, it may act as a nucleator also there. On the other
hand, in many organic systems, where glass is one of the
components, the ability of collagen to act as a nucleator
for apatite crystals is important.

20 When glass comes into contact, for example, with body
fluids, the surface reactions of the glass are induced by a
quick ion exchange as the hydrogen ions and H_3O^+ ions in the
body fluids diffuse onto the surface of the glass, and the
alkaline Na^+ and K^+ ions, in turn, are released from the
25 glass. The network formed by the Si-O-Si bonds of the glass
are broken, but may, if pH is below 9.5, immediately
repolymerise into a silica-rich, gel-like layer on the
surface of the glass. In such a situation, however, the
silica is also always dissolved. If pH is above 9.5, the
30 dissolution is complete. The pH of the surrounding liquid
has a strong effect on ion exchange. Low silica content of
the glass and open structure formed by the silica atom
network, promote rapid exchange of ions. The calcium and
phosphate ions in the glass are diffused through the

19

silica-rich layer; and, they first form an amorphic calciumphophate layer on top of the silica-rich layer. These reactions are initiated within a few minutes when the glass is brought into contact with the liquid. During the
5   days that follow, the silica-rich layer and calciumphosphate layer become gradually thicker. At the same time, amorphic calciumphosphate starts to crystallise into apatite. The formed apatite layer is rich in silica. This is an indirect proof that, in an inorganic system
10 formed by glass and liquid, it is the silica which acts as a nucleator for crystal formation. The above mentioned reactions on the surface of the bioactive glass are illustrated in Figure 11.

The present invention is described in more detail in the
15 following examples.

Example 1

SiO$_2$ (Belgian sand), Na$_2$CO$_3$, CaCO$_3$ and CaHPO$_4$H$_2$O were mixed in the desired proportion and poured into a platinum crucible. The crucible was placed into the oven at 1360°C. After
20 three hours, the crucible was taken out of the oven and the melted composition was poured into clean water. The composition of the resulting crushed glass was equivalent to composition number 4 (S53P4) in Table 1. The glass was immediately removed from the water and rinsed with
25 alcohol. The glass was ground into a fine powder in a ball mill and sifted. Particles below 45 micrometers were collected for future use. The produced glass powder was used in the preparation described in the present invention as follows: the glass powder (1.2 g) was suspended in water
30 (0.4 g) before its application onto the surface of the root of a tooth.

Example 2

The glass powder (S45P7), the composition of which was

equivalent to number 5 in Table 1, was prepared. The same raw materials and methods as in Example 1 were used in the preparation with one exception: the melting time was 2.5 hours at 1340°C. The prepared glass powder was suspended in

5   a physiological saline solution before use.

Example 3

The glass powder (S46PO) of composition number 7 in Table 1 was prepared as described in Example 2. This composition does not contain phophate. The prepared glass powder was

10   suspended in a physiological saline solution before use.

Example 4

The composition described in Example 3 was modified so that Al_2O_3 was replaced with an equivalent amount of SiO_2. Otherwise, the glass powder was prepared as described in

15   Example 3. This composition released silica more rapidly than the composition in Example 3. The prepared glass powder was suspended in a physiological saline solution before use.

Example 5

20   Sodiumsilicate glass powder was prepared according to the method described in Examples 1-4. SiO_2 and Na_2CO_3 were used as raw materials and the glass was melted for 3 hours at 1350°C. The prepared glass powder was suspended in water before use.

25   Example 6

A commercial water glass, i.e. sodiumsilicate solution, was used as such in the preparation of the present invention.

Example 7

A commercial water glass was neutralised with hydrochloric acid. The formed Si-gel was washed with ion-changed water. The Si-gel was dried and the powder was suspended in water
5   before use, as described in Example 1.

Example 8

Preliminary clinical experiment:

Six people (5 women and 1 man), with an average age of 51, participated in the experiment. Four subjects had recently
10   undergone a periodontal flap surgery. All six subjects suffered from tender and hypersensitive dentine. A total of 19 teeth were treated. A bioactive glass powder (S53P4; Table 1; maximum particle size 45 µm) was mixed in a physiological saline solution to form a suspension/paste
15   immediately before use as described in Example 1. The areas to be treated with the preparation were washed and dried carefully. The paste was spread over the area with a foam pad to form a fairly thick layer. The area was covered with a surgical packing (Coe-Pak) for a week. Patients'
20   subjective sensations of pain, measured by using a visual analoque scale (VAS) immediately after the treatment period, was used to assess the reduction of pain. Pain was triggered by using a blast of air and scraping with a probe. The degree of pain was measured at one end of the
25   scale as severe pain and as no pain at the other end of the scale.

Results:

Figure 12 shows the subjective estimation of pain after the initial treatment. For all the patients, the pain
30   practically vanished after one single treatment. The treatment was repeated for two subjects, after which neither of the patients experienced pain when the tooth

surface was probed or air blast. One patient returned for a post-control check after 3 months. She experienced no more hypersensitivity.

Example 9

5   Small samples extracted from the gingiva in connection with tooth exposure operations, performed on young patients were cultured on a bioactive glass substratum, S53P4. Generally, the tissue samples were found to grow well on the surface of the glass and the tissue culture technique was suitable

10 for studying reactions between bioactive glass and different types of soft tissue. The advantages of tissue cultures are that it is possible to study the reactions of both epithelium and connective tissue simultaneously. When the samples were examined electronmicroscopically,

15 epithelial cells were discovered to have formed an organic attachment i.e. hemidesmosomes, and a structure resembling a basal lamina, against the surface of the glass.

This experiment, published earlier (18), showed that epithelial tissue accepts bioactive glass and adheres to

20 it.

Example 10

CaP-precipitatations found in cultured connective tissue *in vitro*

The tissue cultivation was performed as described in
25 example 9.
Von Kossa staining, which stains the calcium salts, revealed CaP-precipitation extending from the surface of the glass, deep into the connective tissue when examined under the light microscope. Analysis of the sample with a
30 scanning electronmicroscope confirms the histological finding: collagen fibrils of connective tissue are trapped inside the apatite layer growing on the surface of the

glass (Figures 13 and 14).

The element analysis of the samples also shows that Si-ions diffuse deep into the connective tissue.

Example 11

5   *In vitro* experiments on decalcified dentine

An extracted tooth was sliced into 200 μm thick sections and treated with hydrochloric acid to dissolve the inorganic components. Dentinal tubules became open as the highly mineralised intratubular dentine dissolved away. The

10   remaining matrix was soft and contained nearly pure Type I collagen, the same as, for example, the connective tissue of the oral mucosa. By using the tissue culture technique described in Example 9, dentine was incubated for 5 days in the culture. The glass (S53P4) and collagen were not found

15   to adhere to each other, but as the collagen sample was bent manually, it felt rigid, as did the dentine section before the acid treatment. When studied under light microscope, it was discovered that the section had remineralised at the depth of 100—150 μm. The dentinal

20   tubules near the surface of the glass, were fully mineralised (Figures 15 and 16).

This experiment shows that bioactive silica containing glass acts as a vehicle which can be used to mineralise collagen structures and close the dentinal tubules in the

25   dentine. The experiment clearly shows that it is possible to strenhthen tooth tissue with the preparation according to the present invention when it is used in association with root canal therapy and filling of a tooth. The experiment further shows that with the help of the

30   preparation of the present invention, it is possible to harden collagen and prepare an agent suitable for a bone substitute or for another type of preparation which can be implanted in living tissues.

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Example 12

In vivo experiments in rats

Experimental periodontal bone defects were made palatally
beside the molars in upper jaws of rats. Bioactive glass
5   (composition = S53P4 in Table 1) powder (granule size
250—315 μm) mixed in a saline solution was applied to one
side of the jaw, the other side serving as a control. To
initiate the healing process of the bone defect, bioactive
glass was allowed to act for 3 weeks. Soft tissue appeared
10   to be similar both on experimental and control sides.
Epithelium readhered onto the surface of the tooth, and
connective tissue did not show infiltration of inflammatory
cells. The material was found to be biocompatible at this
location.

15   This experiment demonstrated tissue compatibility of the
material *in vivo*.

It will apparent to the experts in the field that the
embodiments of the present invention may take different
forms in the scope of the claims presented hereinafter.

25

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CLAIMS

1. Novel use of bioactive silica containing glass, characterized in that said glass is used in the mnanufacture of a preparation useful to reduce pulpal irritation and/or strengthen the tooth structure.

5   2. The use according to claim 1, characterized in that the bioactive silica containing glass is used in the form of a powder, paste, suspension or solution with a physiologically suitable liquid, or is bound to a physiologically suitable vehicle.

10 3. The use according to claim 1 or 2, characterized in that the bioactive silica containing glass includes calcium and phosphate ions, or that calcium and phosphate providing sources are added to the preparation.

4. A pharmaceutical preparation reducing the pulpal
15 irritation of a tooth and/or strengthening the structure of a tooth, characterized in that the glass phase including bioactive silica containing glass has been mixed with
- a physiologically suitable liquid to form a paste, suspension or solution, or
20 - a physiologically suitable binder, such as fibrinogen or chitin which yields a preparation which is moist enough to maintain chemical interactions between the glass phase and dentine thus enabling the transfer of silica into the dentine tissue.

25 5. The preparation according to claim 4, characterized in that it comprises calcium and phosphates sources.

6. The preparation according to claim 4 or 5, characterized in that said preparation comprises an agent promoting the growth of crystals in the target tissue.

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7. The preparation according to claim 4, 5 or 6, **characterized** in that the glass phase
- is solely Si-oxide or Si-hydroxide such as silica gel, or
- comprises in addition to Si-oxide or Si-hydroxide, one or more of the following elements: Na, K, Ca, Mg, B, Ti, Al, P, N or F, or
- is a solution comprising Si-OH-groups.

8. The preparation of claim 7, **characterized** in that the composition of the glass phase is as follows:

SiO_2 or Si-gel	1 - 100%
CaO	0 - 40%
P_2O_5	0 - 60%
Na_2O	0 - 45%
K_2O	0 - 45%
MgO	0 - 40%

9. The preparation of claim 7, **characterized** in that the composition of the glass phase is as follows: SiO_2 53%; CaO 20%; P_2O_5 4% and Na_2O 23%.

10. The preparation of claim 7, **characterized** in that the composition of the glass phase is as follows: SiO_2 45%; CaO 22%; P_2O_5 7%; Na_2O 24% and B_2O_3 2%.

11. The preparation of any of the preceding claims, **characterized** in that the preparation comprises ceramic powder.

ENAMEL

DENTINE

PULP

ODONTOBLASTS

GUM

CEMENTUM

PERIPHERAL
NERVOUS PLEXUS

DENTINE

OUTER SURFACE
OF DENTINE

DENTINAL TUBULE

ODONTOBLAST
PROCESS

FIG. 1

EXPOSED DENTINE SURFACE

INTRATUBULAR DENTINE

FIG. 2

PULP   DENTINE

PAIN

OUTWARD FLOW

INWARD FLOW

NERVOUS PLEXUS

FIG. 3

ENAMEL

DENTINE

PULP

EXPOSED DENTINE
SURFACE

CLEANED PERIDONTAL
POCKET

GUM

CEMENTUM

ALVEOLAR BONE
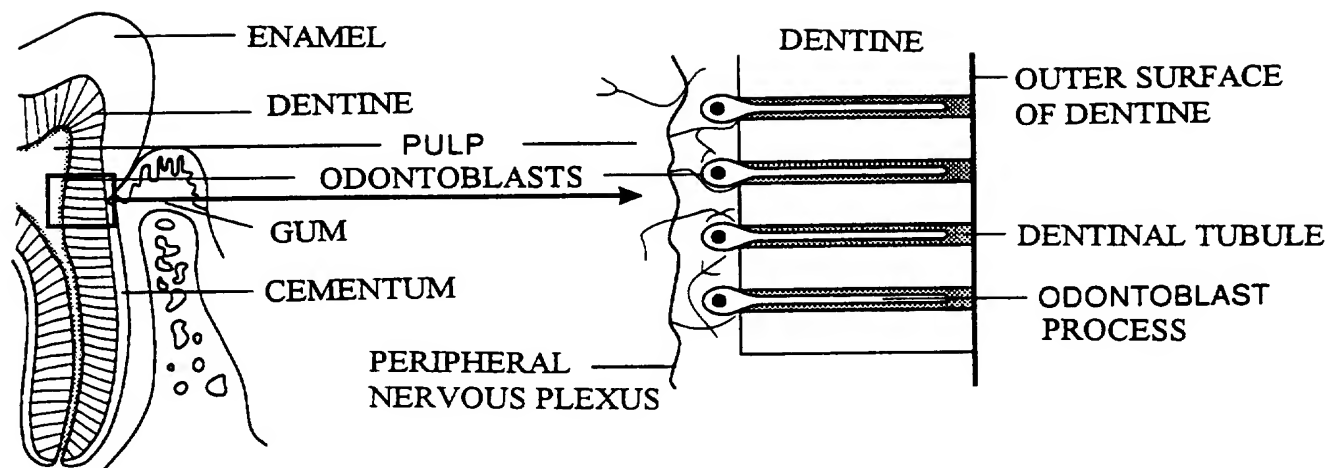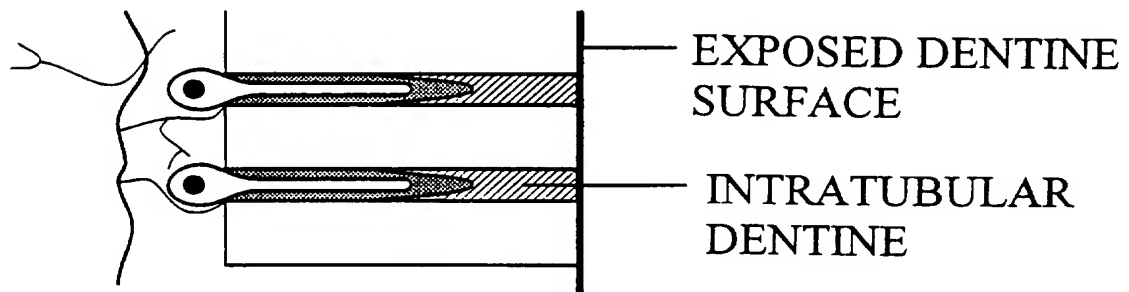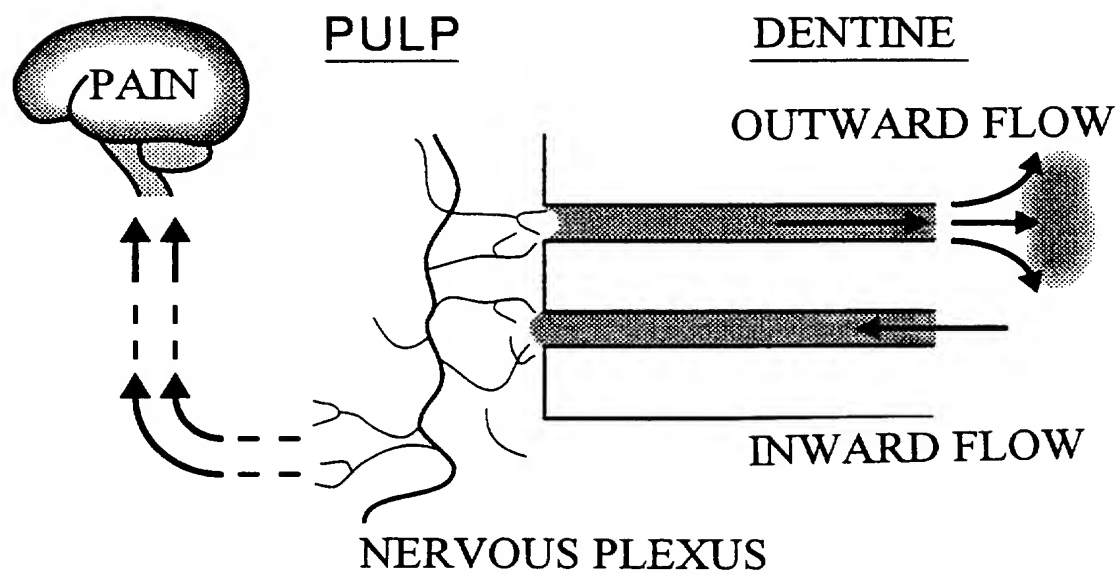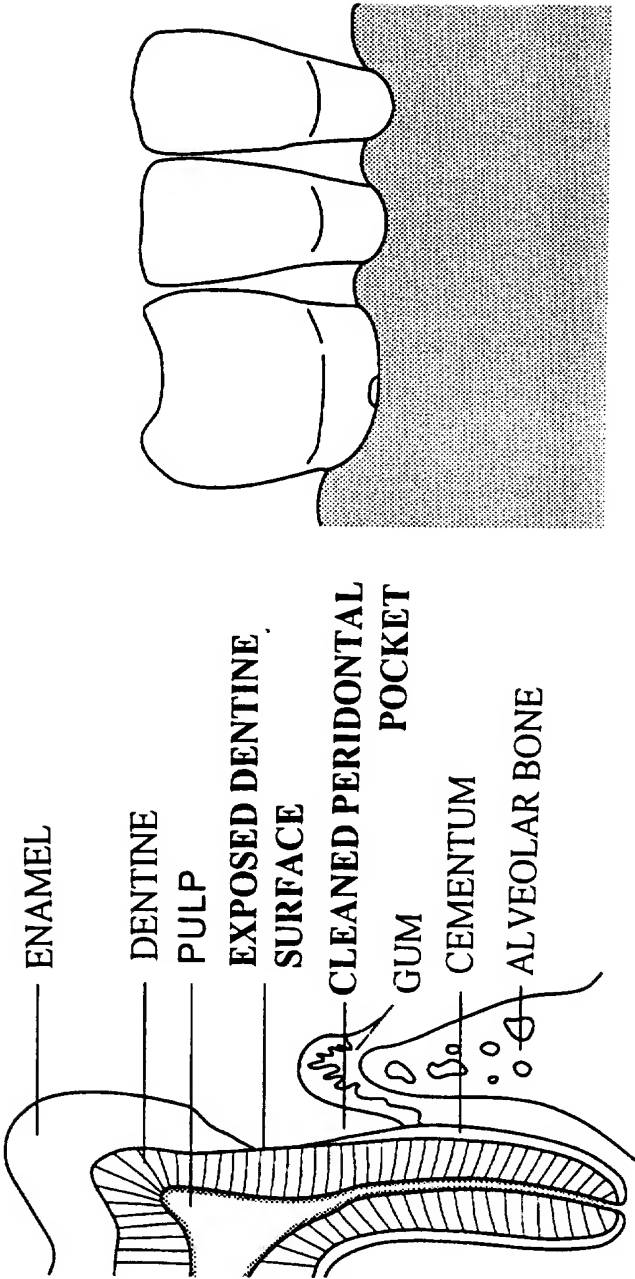
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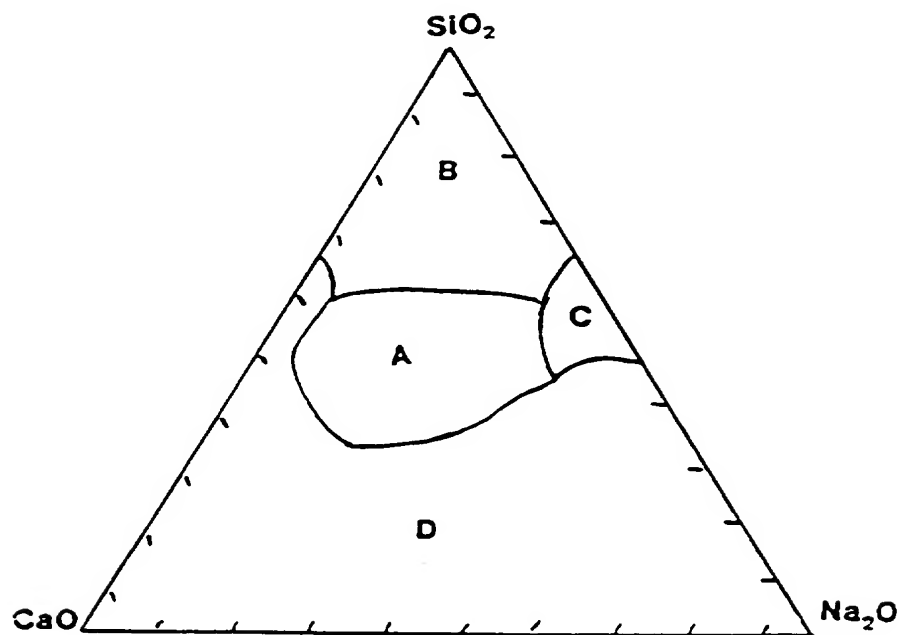
A = BIOACTIVE AREA

B = INERT AREA

C = SOLUBLE GLASS

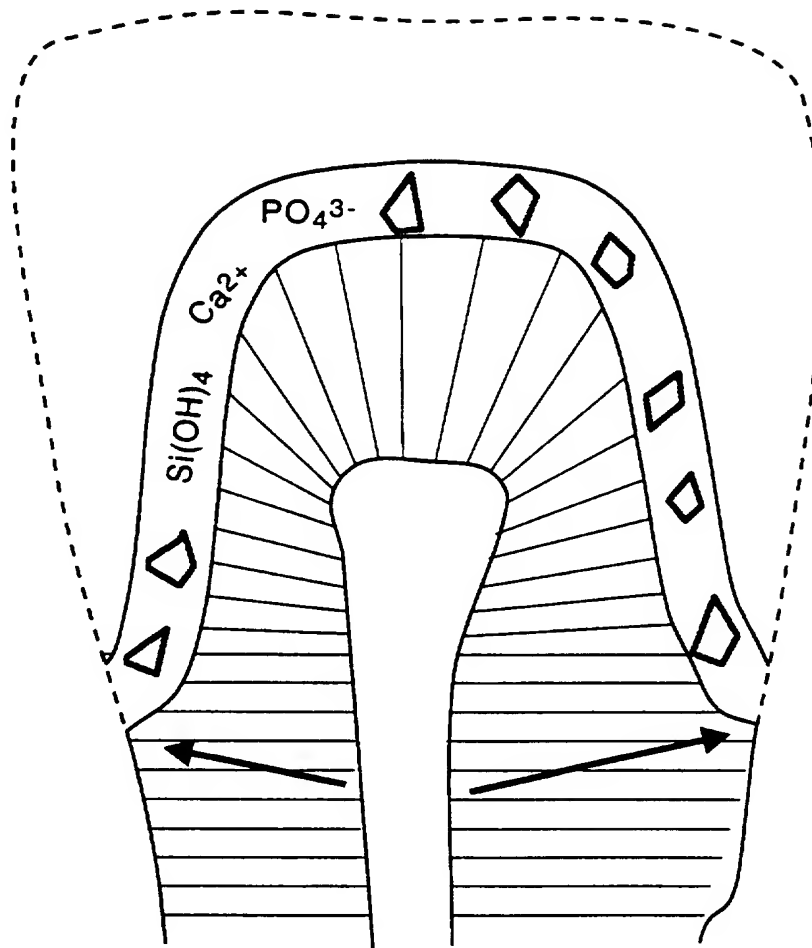D = NO GLASS FORMATION
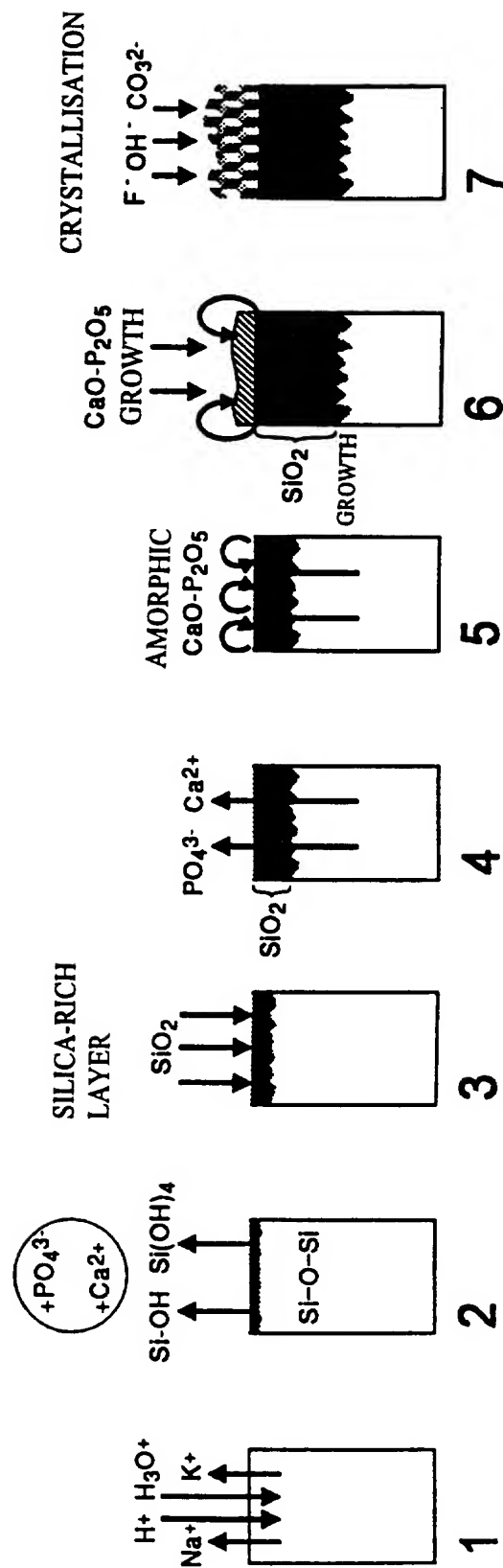
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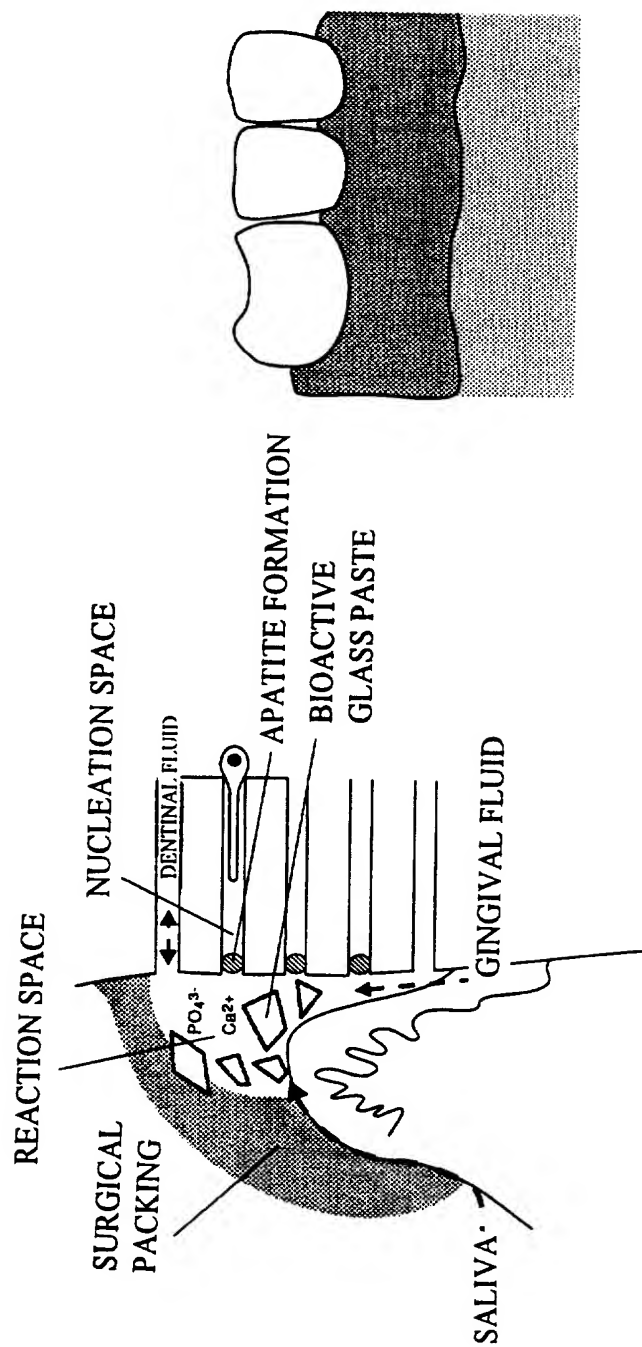
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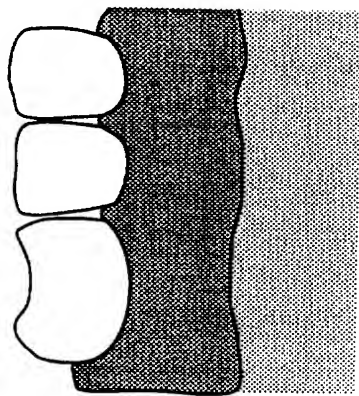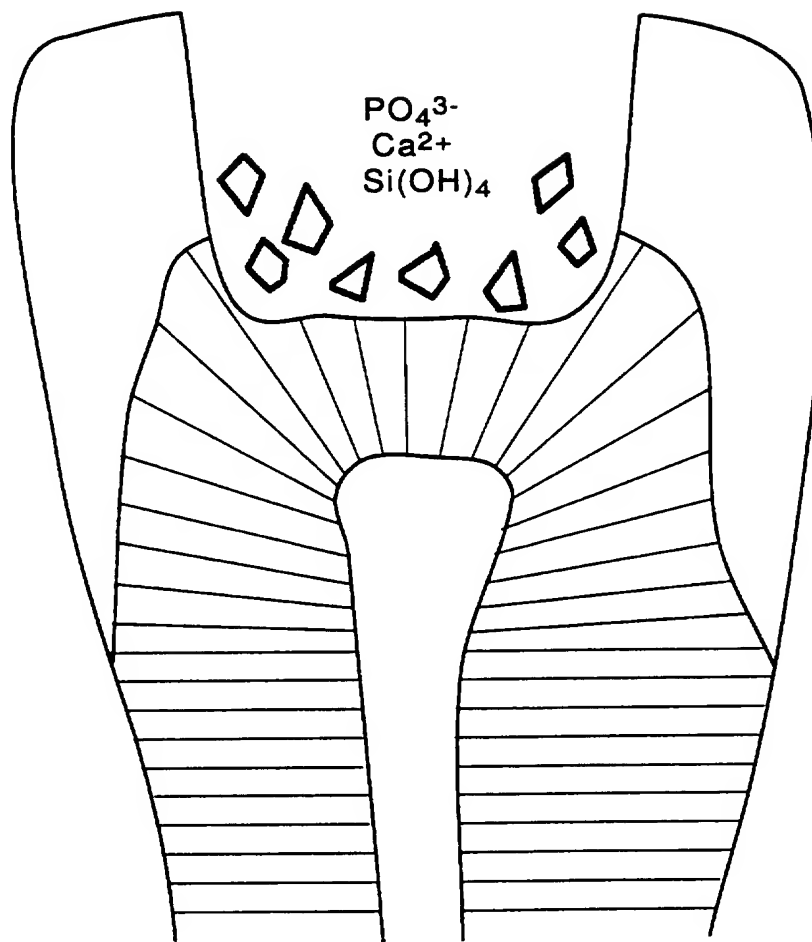
FIG. 7
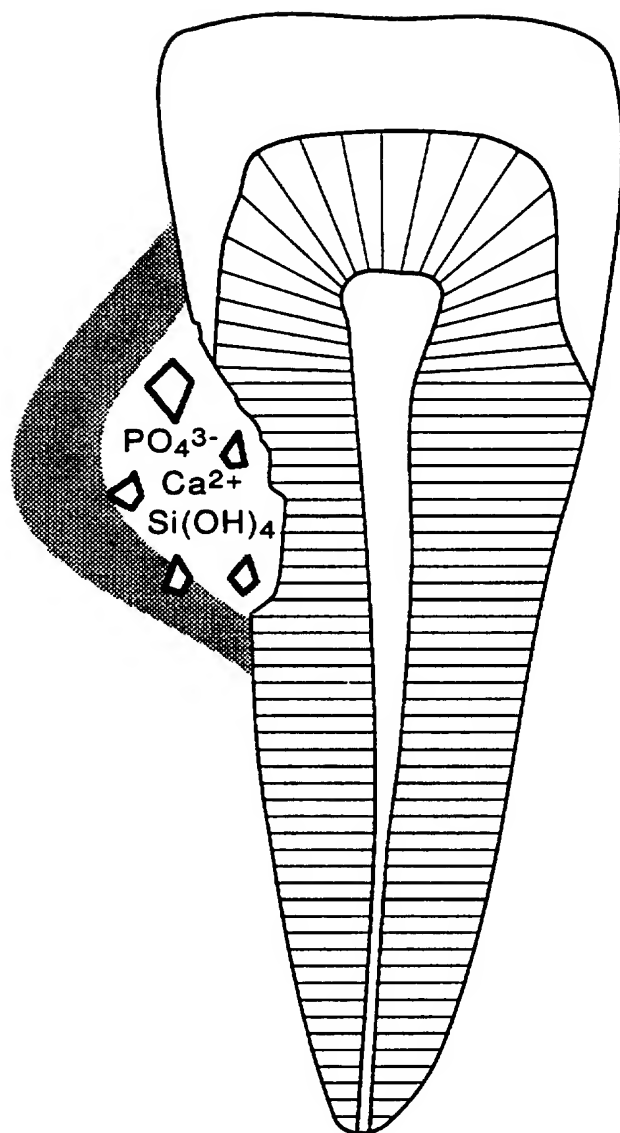
FIG. 8
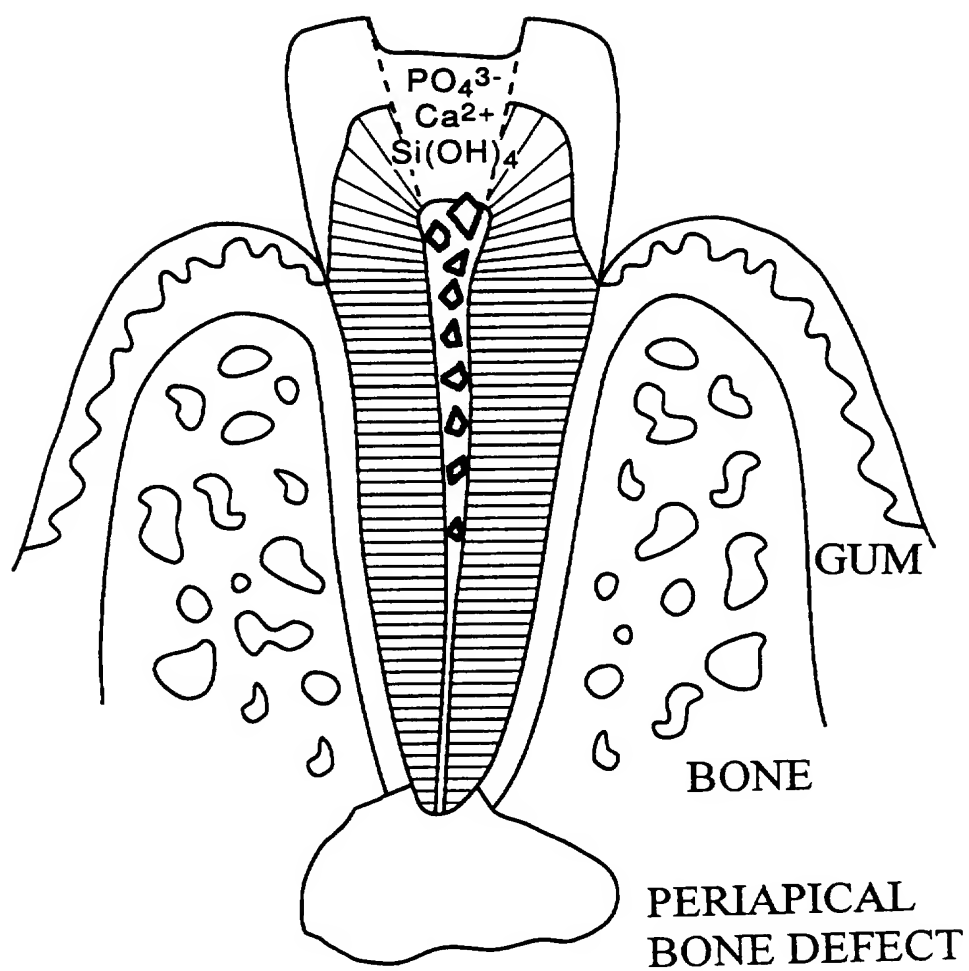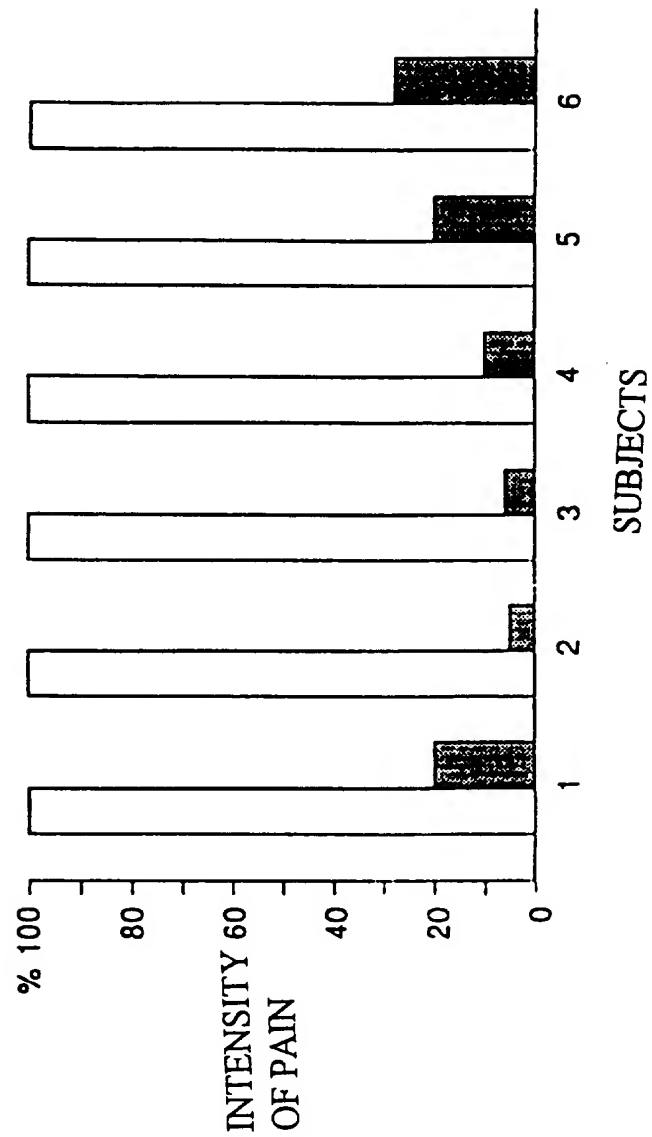
FIG. 9

FIG. 10

REACTIONS ON GLASS SURFACE

FIG. 11

FIG. 12
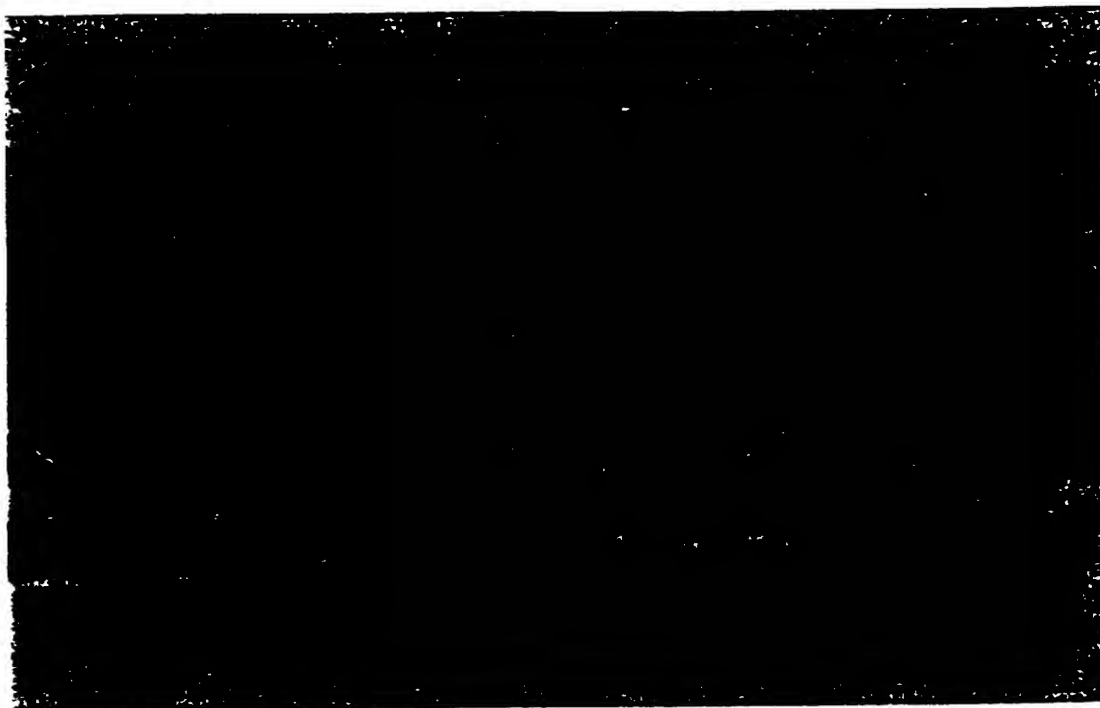
FIG. 13

FIG. 14

FIG. 15
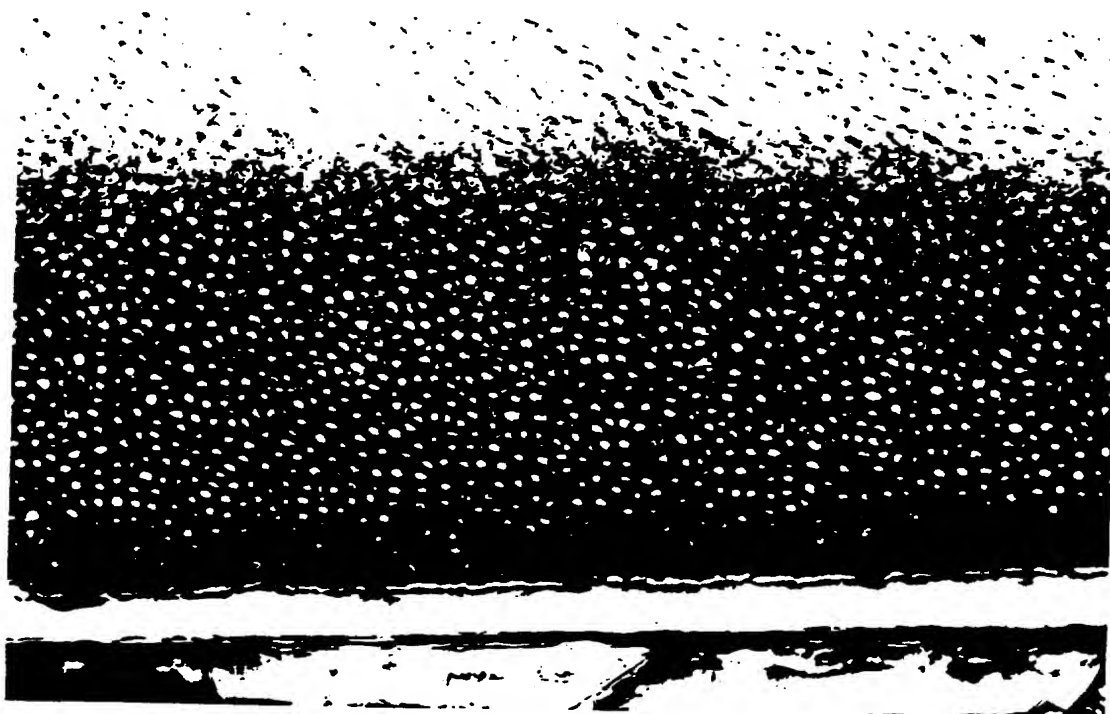

FIG. 16

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 6/027, A61L 25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9117777 A2 (UNIVERSITY OF FLORIDA), 28 November 1991 (28.11.91), abstract; claims 1,4, 22; fig 4	1-11
	--	
X	EP 0511868 A2 (ONODA CEMENT COMPANY, LTD), 4 November 1992 (04.11.92), page 5, line 35 - line 38, abstract	1-11
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A	WO 9320858 A1 (FIDIA S.P.A.), 28 October 1993 (28.10.93), page 3, line 2 - line 22, abstract	1-11
	--	

☐ Further documents are listed in the continuation of Box C.   ☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	
"E" erlier document but published on or after the international filing date	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 1996	15.01.1996
Name and mailing address of the ISA/	Authorized officer
Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Jack Hedlund Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO-A2-	9117777	28/11/91	NONE		
EP-A2-	0511868	04/11/92	JP-A- US-A- JP-A-	4329961 5304577 5023389	18/11/92 19/04/94 02/02/93
WO-A1-	9320858	28/10/93	NONE		